

Peripheral arterial disease of the lower extremities

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Submitted: 1 September 2011

Accepted: 17 October 2011

Arch Med Sci 2012; 8, 2: 375-388

DOI: 10.5114/aoms.2012.28568

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Abstract

Persons with peripheral arterial disease (PAD) are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from coronary artery disease. Smoking should be stopped and hypertension, dyslipidemia, diabetes mellitus, and hypothyroidism treated. Statins reduce the incidence of intermittent claudication and improve exercise duration until the onset of intermittent claudication in persons with PAD and hypercholesterolemia. The serum low-density lipoprotein cholesterol should be reduced to < 70 mg/dl. Antiplatelet drugs such as aspirin or clopidogrel, angiotensin-converting enzyme inhibitors, and statins should be given to persons with PAD. β -Blockers should be given if coronary artery disease is present. Cilostazol improves exercise time until intermittent claudication. Exercise rehabilitation programs should be used. Revascularization should be performed if indicated.

Key words: peripheral arterial disease, antiplatelet drugs, statins, exercise, revascularization.

Introduction

Peripheral arterial disease (PAD) is chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. The PAD may cause intermittent claudication which is pain or weakness with walking that is relieved with rest. The muscle pain or weakness after exercise occurs distal to the arterial obstruction. Since the superficial femoral and popliteal arteries are most commonly affected by atherosclerosis, the pain of intermittent claudication is most commonly localized to the calf. Atherosclerotic obstruction of the distal aorta and its bifurcation into the two iliac arteries may cause pain in the buttocks, hips, thighs, or the inferior back muscles as well as the calves.

The Rutherford classification of PAD includes 7 stages [1]. Table I lists these 7 stages. Only one-half of elderly persons with documented PAD are symptomatic. Persons with PAD may not walk far or fast enough to induce muscle ischemic symptoms because of comorbidities such as pulmonary disease or arthritis, may have atypical symptoms unrecognized as intermittent claudication [2], may fail to mention their symptoms to their physician, or may have sufficient collateral arterial channels to tolerate their arterial obstruction. Women with PAD have a higher prevalence of leg pain on exertion and at rest, poorer functioning, and greater walking impairment from leg symptoms than men with PAD [3]. Poorer leg strength in women contributes to poorer lower extremity functioning in women with PAD than in men with PAD [3]. Women with PAD experience faster func-

Table I. Rutherford classification of peripheral arterial disease [1]

Stage 0 if the patient is asymptomatic
Stage 1 if mild intermittent claudication is present
Stage 2 if moderate intermittent claudication is present
Stage 3 if severe intermittent claudication is present
Stage 4 if ischemic rest pain is present
Stage 5 if the patient has minor tissue loss
Stage 6 if the patient has ulceration or gangrene

tional decline than men with PAD [4]. Greater sedentary hours and slower outdoor walking speed are associated with faster declines in functioning and adverse calf muscle changes in PAD [5]. Higher physical activity levels during daily life are associated with less functional decline in persons with PAD [6].

If the arterial flow to the lower extremities cannot meet the needs of resting tissue metabolism, critical lower extremity ischemia occurs with pain at rest or tissue loss. Critical ischemia causes rest pain in the toes or foot with progression to ulceration or gangrene. Chronic arterial insufficiency ulcers commonly develop at the ankle, heel, or leg. Mummified, dry, black toes or devitalized soft tissue covered by a crust is gangrene caused by ischemic infarction. Suppuration often develops with time, and dry gangrene changes to wet gangrene.

Physical examination

The vascular physical examination includes the components described in Table II.

Noninvasive diagnosis

Persons with PAD of the lower extremities have decreased or absent arterial pulses. Noninvasive

Table II. Vascular physical examination (adapted from [7])

1. Measurement of blood pressure in both arms
2. Palpation of carotid pulses and listening for carotid bruits
3. Auscultation of abdomen and flank for bruits
4. Palpation of abdomen and notation of presence of aortic pulsation and its maximal diameter
5. Palpation of pulses at the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial sites
6. Auscultation of both femoral arteries for femoral bruits
7. Remove shoes and socks and inspect feet
8. Evaluate color, temperature, and integrity of skin
9. Note presence of distal hair loss, trophic skin changes, hypertrophic nails, and ulcerations

tests used to assess lower extremity arterial blood flow include measurement of ankle and brachial artery systolic blood pressures, characterization of velocity wave form, and duplex ultrasonography. Measurement of ankle and brachial artery systolic blood pressures using a Doppler stethoscope and blood pressure cuffs allows calculation of the ankle-brachial index (ABI) which is normally 0.9 to 1.2. An ABI of less than 0.90 is 95% sensitive and 99% specific for the diagnosis of PAD [8]. The lower the ABI, the more severe the restriction of arterial blood flow, and the more serious the ischemia. The ABIs of 0.6 to 0.9 usually correlate with mild to moderate intermittent claudication. The ABIs of 0.4 to 0.6 usually correlate with severe intermittent claudication. With ABIs between 0.25 to 0.4, rest pain and tissue loss are often found. Patients with calcified arteries from diabetes mellitus or renal failure occasionally have relatively non-compressible arteries leading to falsely elevated ABI values in the normal range. Persons with an ABI of 1.4 or higher also have an increased incidence of cardiovascular events [9] and lower quality of life [10].

In addition to measuring arterial pressure in non-palpable arteries, Doppler ultrasound methods allow characterization of the flow versus time velocity waveform. Finding biphasic flow at the groin or monophasic flow more distally is evidence of arterial obstruction even when ABI measurements are falsely increased to normal levels because of calcification.

Duplex ultrasonography combines Doppler frequency measurements with two-dimensional images of blood vessels. The severity of flow restriction caused by an arterial stenosis can be accurately assessed by this most comprehensive noninvasive method [11]. Duplex ultrasonography, computed tomographic angiography, and magnetic resonance angiography are useful in assessing the anatomic location and severity of PAD and in selecting suitable candidates for endovascular or surgical revascularization [7].

Treadmill exercise testing with and without pre-exercise and postexercise ABIs helps differentiate claudication from pseudoclaudication in patients with exertional leg symptoms [7]. Treadmill exercise testing may be useful to diagnose PAD with a normal resting ABI but a reduced postexercise ABI [7]. Treadmill exercise testing may objectively document the magnitude of symptom limitation in patients with claudication [7]. The postexercise ABI is a powerful independent predictor of all-cause mortality and provides additional risk stratification than the resting ABI [12]. Patients with coronary artery disease (CAD) scheduled for coronary artery bypass graft surgery with PAD should have routine carotid artery duplex ultrasonography to screen for carotid arterial disease.

Prevalence

The prevalence of PAD increases with age. Schroll and Munck reported that the prevalence of PAD was 16% in men and 13% in women aged 60 years [13]. Criqui *et al.* showed that the prevalence of PAD was 5.6% in persons aged 38 to 59 years, 15.9% in persons aged 60 to 69 years old, and 33.8% in persons aged 70 to 82 years old [14]. In the Cardiovascular Health Study, PAD was present in 13.9% of 2,214 men aged ≥ 65 years and in 11.4% of 2,870 women aged ≥ 65 years without cardiovascular disease [15]. Symptomatic PAD was present in 20% of 467 men, mean age 80 years, and in 13% of 1,444 women, mean age 81 years, living in the community and being seen in a geriatrics clinic [16]. In the Rotterdam Study, PAD was present in 16.9% of 2,589 men aged ≥ 55 years and in 20.5% of 3,861 women aged ≥ 55 years [17]. The prevalence of symptomatic PAD was 32% in 1,160 men, mean age 80 years, and 26% in 2,464 women, mean age 81 year, living in a nursing home [18]. The prevalence of symptomatic PAD in persons living in a nursing home was also 29% in 268 blacks, mean age 81 years, 24% in 71 Hispanics, mean age 81 years, and 23% in 1,310 whites, mean age 82 years [19]. The prevalence of symptomatic PAD was 26.7% in 386 men, mean age 72 years, and 17.1% in 620 women, mean age 72 years, living in the community and being seen in a university general medicine clinic [20]. The prevalence of PAD in 6,979 men and women, mean age 69 years, screened for PAD by an ABI because they were aged 70 years or older or because they were aged 50-69 years with a history of cigarette smoking or diabetes mellitus was 29% [21]. Among these patients with PAD, classic claudication was present in only 11% [21].

Risk factors

Modifiable risk factors that predispose to PAD include cigarette smoking [13, 16, 20, 22-30], diabetes mellitus [13, 16, 20, 22-29, 31], hypertension [13, 14, 16, 20, 26-29, 32], dyslipidemia [13, 16, 20, 22, 24-29, 31, 33-35], increased plasma homocysteine levels [36-39], and hypothyroidism [40]. Obesity was associated with a high ABI [41]. A reduced glomerular filtration rate [42-44] and microalbuminuria [44] are associated with PAD.

Significant independent risk factors for PAD in 467 men, mean age 80 years, and in 1,444 women, mean age 81 years, living in the community and seen in an academic geriatrics practice were age (odds ratio = 1.05 for each 1-year increase in age in men and 1.03 for each 1-year increase in age in women); current cigarette smoking (odds ratio = 2.6 for men and 4.6 for women); systolic or diastolic hypertension (odds ratio = 2.2 for men and 2.8 for women); diabetes mellitus (odds ratio = 6.1 for

men and 3.6 for women); serum high-density lipoprotein cholesterol (odds ratio = 0.95 for each 1 mg/dl increase in men and 0.97 for each 1 mg/dl increase in women); and serum low-density lipoprotein (LDL) cholesterol (odds ratio = 1.02 for each 1 mg/dl increase in men and in women) [16].

In 147 men and women with PAD and 373 men and women without PAD, mean age 81 years, plasma homocysteine was a significant independent risk factor for PAD with an odds ratio of 1.13 for each 1 $\mu\text{mol/l}$ increase [39]. In 249 men and women, mean age 79 years, the prevalence of PAD was significantly higher in persons with subclinical hypothyroidism (14 of 18 persons or 78%) than in persons with euthyroidism (40 of 231 persons or 17%) [40]. Elevated plasma glucose and white blood cell count have also been found to increase the risk of PAD in asymptomatic diabetics [45].

Coexistence of other atherosclerotic disorders

The PAD coexists with other atherosclerotic disorders [14, 23, 35-40]. In a study of 1,886 men and women, mean age 81 years, 270 of 468 persons (58%) with PAD had coexistent CAD and 159 of 468 persons (34%) with PAD had prior ischemic stroke [46]. The CAD was diagnosed as previously described [47-52]. Ischemic stroke was diagnosed as previously described [52-55]. In a study of 1,802 men and women, mean age 80 years, living in the community and seen in an academic geriatrics practice, 161 of 236 persons (68%) with PAD had coexistent CAD and 100 of 236 persons (42%) with PAD had coexistent prior ischemic stroke [56].

In 924 men, mean age 80 years, the prevalence of PAD was 1.5 times significantly higher in 336 men with mitral annular calcium than in 588 men without mitral annular calcium (43% vs. 28%) [56]. In 1,881 women, mean age 81 years, the prevalence of PAD was 1.6 times significantly higher in 985 women with mitral annular calcium than in 896 women without mitral annular calcium (31% vs. 19%) [57].

In 989 men, mean age 80 years, the prevalence of PAD was 1.6 times significantly higher in 141 men with valvular aortic stenosis than in 848 men without valvular aortic stenosis (48% vs. 30%) [58]. In 1,998 women, mean age 81 years, the prevalence of PAD was 1.7 times significantly higher in 321 women with valvular aortic stenosis than in 1,677 women without valvular aortic stenosis (39% vs. 23%) [58].

In 279 men and women, mean age 71 years, with documented PAD and in 218 men and women, mean age 70 years, without PAD with normal ABIs undergoing coronary angiography for suspected CAD, the prevalence of obstructive CAD was significantly higher in persons with PAD (98%) than in persons without PAD (81%) [29]. The prevalence of

left main CAD was significantly higher in persons with CAD (18%) than in persons without CAD (< 1%) [29]. The incidence of 3-vessel or 4-vessel CAD was significantly higher in persons with PAD (63%) than in persons without PAD (11%) [29].

In 1,006 men and women, mean age 72 years, if PAD was present, 63% had coexistent CAD, and 43% had prior ischemic stroke [20]. In 118 patients, mean age 73 years, with a decreased ABI, the prevalence of CAD was 75%, whereas in 118 age-matched and gender-matched patients with a normal ABI, the prevalence of CAD was 29% [59]. The prevalence of aortic valve calcium or mitral annular calcium was also higher in the patients with a decreased ABI (69%) than in the patients with a normal ABI (36%) [59].

In 273 patients, mean age 71 years, with CAD, the lower the ABI, the higher the prevalence of 3-vessel or 4-vessel CAD [60]. Patients with PAD and CAD have more extensive and calcified coronary atherosclerosis, constrictive arterial remodeling, and greater disease progression [61]. Patients with PAD also have a higher prevalence of left ventricular systolic dysfunction than patients without PAD [62].

Cardiovascular events and mortality

Persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events [9, 24, 63-78]. At 10-year follow-up of 565 men and women, mean age 66 years, PAD significantly increased the risk of all-cause mortality (relative risk = 3.1), of mortality from cardiovascular disease (relative risk = 5.9), and of mortality from CAD (relative risk = 6.6) [63]. At 4-year follow-up of 1,492 women, mean age 71 years, an ABI of 0.9 or less was associated with a relative risk of 3.1 for all-cause mortality after adjustment for age, smoking, and other risk factors [64]. At 5.3-year follow-up of 6, 647 persons living in the community, an ABI < 1.0 increased cardiovascular events 1.77 times, and an ABI of 1.40 or higher increased cardiovascular events 1.85 times [9].

In a prospective study of 291 men and women, mean age 82 years, with PAD, CAD was present in 160 persons (55%) [56]. Silent myocardial ischemia detected by 24-h ambulatory electrocardiography was present in 60 of 160 persons (38%) with PAD and CAD and in 26 of 131 persons (20%) with PAD and no clinically evident CAD [65]. At 43-month follow-up, new coronary events developed in 54 of 60 persons (90%) with PAD, CAD, and silent myocardial ischemia and in 59 of 100 persons (59%) with PAD, CAD, and no silent myocardial ischemia [65]. New coronary events also developed in 18 of 26 persons (69%) with PAD, no CAD, and silent myocardial ischemia and in 34 of 105 persons (32%) with PAD, no CAD, and no silent myocardial ischemia [65].

A pooled analysis of mortality in 8 large randomized percutaneous coronary intervention (PCI) trials of 19, 867 patients showed that the presence of PAD was associated with higher rates of post-PCI death and myocardial infarction [71]. The PAD was an independent predictor of short-term and of long-term mortality [71].

At 7.5-year follow-up of persons in the Cardiovascular Health study in a propensity-matched study of community dwelling older adults, matched hazard ratios for PAD for all-cause mortality, incident heart failure, and symptomatic PAD were 1.57, 1.32, and 3.92, respectively [74]. In a well-balanced propensity-matched population of 2689 patients with advanced chronic systolic heart failure, during 4.1 years of follow-up, PAD was significantly associated with increased mortality and hospitalization [77].

Dipyridamole thallium scintigraphy also has prognostic value in the preoperative assessment of patients with PAD undergoing vascular surgery [79].

Risk factor modification

Continuing smoking increases the risk of amputation in patients with intermittent claudication [80]. Patency in lower extremity bypass grafts is also worse in smokers than in nonsmokers [81]. Smoking cessation decreases progression of PAD to critical leg ischemia and reduces the risk of myocardial infarction and death from vascular causes [82]. Smokers should be referred to a smoking cessation program (Table III).

Approaches to smoking cessation include use of nicotine patches or nicotine polacrilex gum, which are available over the counter [83]. If this therapy is unsuccessful, nicotine nasal spray or treatment with the antidepressant bupropion should be considered [83, 84]. A nicotine inhaler may also be used [85]. The dosage and duration of treatment of each of these pharmacotherapies are discussed in detail elsewhere [85]. Varenicline may also be used [86]. Concomitant behavioral therapy may also be needed [87]. Repeated physician advice is very important in the treatment of smoking addiction.

Hypertension should be adequately controlled to reduce cardiovascular mortality and morbidity in persons with PAD [32, 88-90] (Table III). The blood pressure should be reduced to < 140/90 mm Hg [32]. In the Heart Outcomes Prevention Evaluation (HOPE) Study, 1715 persons had symptomatic PAD, and 2118 persons had asymptomatic PAD with an ABI less than 0.9 [89]. In the HOPE Study, compared with placebo, ramipril 10 mg daily significantly reduced cardiovascular events by 25% in persons with symptomatic PAD [89]. In this study, ramipril reduced the absolute incidence of cardiovascular events by 5.9% in persons with asymptomatic PAD and by 2.3% in persons with a normal ABI [89]. In

the HOPE Study, the antihypertensive properties of ramipril did not completely account for the observed risk reduction [89].

Among persons with PAD in the Appropriate Blood Pressure Control in Diabetes trial, the incidence of cardiovascular events in persons treated with antihypertensive drug therapy with enalapril or nisoldipine was 13.6% if the mean blood pressure was reduced to 128/75 mm Hg vs. 38.7% if the mean blood pressure was reduced to 137/81 mm Hg [90].

Elderly persons with diabetes mellitus and PAD and no CAD have a 1.5 times higher incidence of new coronary events than elderly nondiabetics with PAD and prior MI [91]. The higher the hemoglobin A_{1c} levels in patients with diabetes mellitus and PAD, the higher the prevalence of severe PAD [92]. Diabetes mellitus should be treated with the hemoglobin A_{1c} level decreased to less than 7.0% to decrease the incidence of myocardial infarction [93]. Some guidelines recommend lowering the blood pressure in diabetics to < 130/80 mm Hg based on expert medical opinion [94]. Elderly diabetics with PAD should also be treated with statins [95] and the serum low-density lipoprotein (LDL) cholesterol reduced to < 70 mg/dl [96].

Treatment of dyslipidemia with statins has been documented to reduce the incidence of mortality, cardiovascular events, and stroke in persons with PAD with and without CAD [34, 35, 96-104]. At 5-year follow-up of 4,444 men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin significantly decreased the incidence of intermittent claudication by 38% [97].

In a study of 264 men and 396 women, mean age 80 years, with symptomatic PAD and a serum LDL cholesterol of 125 mg/dl or higher, 318 of 660 persons (48%) were treated with a statin and 342 of 660 persons (52%) with no lipid-lowering drug [102]. At 39-month follow-up, treatment with statins caused a significant independent reduction in the incidence of new coronary events of 58%, of 52% in persons with prior myocardial infarction, and of 59% in persons with no prior myocardial infarction [102].

In the Heart Protection Study, 6748 of the 20536 persons (33%) had PAD [98]. At 5-year follow-up, treatment with simvastatin 40 mg daily caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independent of age, gender, or serum lipids levels [98]. These data favor administration of statins to elderly persons with PAD regardless of serum lipids levels. The Heart Protection Study also reported that simvastatin reduced in patients with PAD the rate of first major vascular events by about one-quarter and that of peripheral vascular events by about one-sixth, with large absolute benefits seen in

Table III. Management of peripheral arterial disease

1. Refer to smoking cessation program
2. Treatment of hypertension with blood pressure reduced to < 140/90 mm Hg
3. Control diabetes mellitus with the hemoglobin A _{1c} level reduced to < 7.0%
4. Treat dyslipidemia and reduce serum low-density lipoprotein cholesterol to < 70 mg/dl
5. Antiplatelet drug therapy with aspirin or clopidogrel
6. Treatment with an angiotensin-converting enzyme inhibitor
7. Treatment with β -blockers in patients with coronary artery disease in the absence of contraindications to these drugs
8. Use of statins
9. Treatment with cilostazol in patients with intermittent claudication
10. Exercise rehabilitation program
11. Foot care
12. Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are: <ul style="list-style-type: none"> • incapacitating claudication in persons interfering with work or lifestyle; • limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; • vasculogenic impotence
13. Amputation of lower extremities should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage

patients with PAD because of their high vascular risk [104].

On the basis of the available data, elderly persons with PAD and hypercholesterolemia should be treated with statins to reduce cardiovascular mortality and morbidity and progression of PAD [34, 35, 94-104] and to improve exercise time until intermittent claudication [105-107] (Table III). Statins also reduce perioperative myocardial infarction and mortality [108, 109] and 2-year mortality [109] in patients undergoing noncardiac vascular surgery.

Although 3 double-blind, randomized, placebo-controlled studies demonstrated that statins improve exercise time until intermittent claudication [105-107], one observational study which was not placebo-controlled showed in 68 patients with PAD that despite effective lowering of serum low-density lipoprotein cholesterol by simvastatin or ezetimibe, neither tissue perfusion, metabolism, nor exercise parameters improved, although resting ABI did [110].

Since lipid-lowering therapy is underutilized in persons with PAD [111, 112], intensive educational programs are needed to educate physicians to use lipid-lowering therapy in elderly persons with cardiovascular disease and dyslipidemia [112-114]. On the basis of data from the Heart Protection Study, persons with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels [98].

Increased plasma homocysteine level is a risk factor for PAD [30-33]. Reduction of increased plasma homocysteine levels can be achieved by administering a combination of folic acid, vitamin B₆, and vitamin B₁₂. However, we do not have double-blind, randomized, placebo-controlled data showing that reduction of increased plasma homocysteine levels will reduce coronary events and slow progression of PAD in elderly persons with PAD.

Hypothyroidism is a risk factor for PAD [40]. Elderly persons with clinical or subclinical hypothyroidism should be treated with l-thyroxine to decrease the development of CAD [115] and possibly of PAD [40]. There is no evidence showing that treatment with l-thyroxine will reduce the development of PAD or improve symptoms.

Antiplatelet drugs

Antiplatelet drugs that have been shown to reduce the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke in persons with PAD are aspirin, ticlopidine and clopidogrel [116]. Aspirin plus dipyridamole has not been shown to be more efficacious than aspirin alone in the treatment of persons with PAD [116]. Oral platelet glycoprotein IIb/IIIa inhibitors have been shown to increase mortality in the treatment of persons with CAD and have not been investigated in the treatment of persons with PAD [117]. Adverse hematologic effects associated with ticlopidine limit the use of this drug in the treatment of elderly persons with PAD [118].

Thromboxane A₂ induces platelet aggregation and vasoconstriction. Aspirin decreases the aggregation of platelets exposed to thrombogenic stimuli by inhibiting the cyclooxygenase enzyme reaction within the platelet and thereby blocking the conversion of arachidonic acid to thromboxane A₂ [119]. Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting the binding of adenosine 5'-diphosphate to its platelet receptor [120].

The Antithrombotic Trialists' Collaboration Group (ATCG) reported a meta-analysis of 26 randomized studies of 6,263 persons with intermittent claudication due to PAD [116]. At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 6.4% in patients randomized to antiplatelet drugs vs. 7.9% in the control group, a significant reduction of 23% caused by

antiplatelet therapy. The reductions are significant for all subgroups.

The ATCG reported a meta-analysis of 12 randomized studies of 2,497 persons with PAD undergoing peripheral arterial grafting [116]. At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 5.4% in persons randomized to antiplatelet drugs vs. 6.5% in the control group, a significant reduction of 22% caused by antiplatelet therapy.

The ATCG also reported a meta-analysis of 4 randomized studies of 946 persons with PAD undergoing peripheral angioplasty [116]. At follow-up, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 2.5% in patients randomized to antiplatelet drugs vs. 3.6% in the control group, a significant reduction of 29% caused by antiplatelet therapy.

If one combines the 42 randomized studies of 9,706 patients with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke at follow-up was significantly reduced 23% by antiplatelet drugs, with similar benefits among patients with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty [116]. These data favor the use of aspirin in men and women with PAD [116] (Table III).

However, the Aspirin for Asymptomatic Atherosclerosis trial showed in 3,350 persons without clinical cardiovascular disease who had an ABI \leq 0.95 based on screening that compared to placebo, aspirin 100 mg daily did not reduce vascular events [121]. A post hoc analysis of the 3,096 patients with PAD in the Clopidogrel for High Atherothrombotic Risk and Ischemic, Management, and Avoidance (CHARISMA) trial showed that the primary endpoint of cardiovascular death or nonfatal myocardial infarction or nonfatal stroke was insignificantly reduced by 15% from 8.9% in patients treated aspirin plus placebo to 7.6% in patients treated with aspirin plus clopidogrel [122].

The reduction in high-risk persons of the incidence of vascular death, nonfatal MI, and nonfatal stroke was 19% in 34 trials using an aspirin dose of 500-1500 mg daily, 26% in 19 trials using an aspirin dose of 160-325 mg daily, 32% in 12 trials using an aspirin dose of 75-150 mg daily, and 13% in 3 trials using an aspirin dose of < 75 mg daily [116]. Since aspirin doses greater than 150 mg daily do not reduce vascular death, nonfatal myocardial infarction, and nonfatal stroke more than does a dose of 75 mg to 150 mg daily and cause more gastrointestinal bleeding than the lower doses, this author prefers an aspirin dose of 81 mg daily in treating elderly persons with atherosclerotic vascular disease.

In the Clopidogrel vs. Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, 5,795 persons with PAD were randomized to clopidogrel 75 mg

daily and 5,797 persons with PAD were randomized to aspirin 325 mg daily [123]. At 1.9-year follow-up, the annual incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 3.7% in persons randomized to clopidogrel vs. 4.9% in persons randomized to aspirin, a 24% significant decrease with the use of clopidogrel [123].

On the basis of these data, it is reasonable to conclude that clopidogrel is superior to aspirin in the management of patients with PAD. However, clopidogrel is much more expensive than is aspirin. In a vascular surgery clinic, 501 of 561 persons (89%) with PAD were treated with aspirin or clopidogrel [124].

Oral anticoagulants

In the Dutch Bypass Oral Anticoagulants or Aspirin Study, 2690 persons were randomized after infrainguinal bypass surgery to aspirin 80 mg daily or to oral anticoagulation with phenprocoumon or acenocoumarol to maintain an INR of 3.0-4.5 [120]. At 21-month follow-up, there was no significant difference between the two treatments in the primary outcome of infrainguinal graft occlusion [125]. There was no significant difference between the two treatments in the secondary outcomes of myocardial infarction, stroke, amputation, or vascular death [125]. However, persons treated with oral anticoagulant therapy had 1.96 times more major bleeding episodes than persons treated with oral aspirin [125]. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines state that oral anticoagulant therapy with warfarin should not be given to decrease the risk of adverse cardiovascular ischemic events in persons with atherosclerotic lower extremity PAD [7].

Angiotensin-converting enzyme inhibitors

Data from the HOPE Study showed that ramipril 10 mg daily significantly decreased cardiovascular events in persons with symptomatic PAD and in persons with asymptomatic PAD [89]. Angiotensin-converting enzyme inhibitors as well as statins also have many pleiotropic effects to account for their vascular protective properties beyond their primary mode of action including inhibition of cellular proliferation, restoration of endothelial activity, inhibition of platelet reactivity, and an antioxidant potential [126]. The ACC/AHA guidelines recommend treating persons with PAD with angiotensin-converting enzyme inhibitors unless there are contraindications to the use of these drugs to reduce cardiovascular mortality and morbidity [127] (Table III).

β -Blockers

Persons with PAD are at increased risk for developing new coronary events [24, 63-78]. Many physi-

cians have been reluctant to use β -blockers in persons with PAD because of concerns that β -blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies found that β -blockers do not adversely effect walking capacity or the symptoms of intermittent claudication in persons with mild-to-moderate PAD [128].

An observational study was performed in 575 men and women, mean age 80 years, with symptomatic PAD and prior myocardial infarction [129]. Of the 575 persons, 85 (15%) had contraindications to the use of β -blockers. Of the 490 persons without contraindications to the use of β -blockers, 257 persons (52%) were treated with β -blockers. Adverse effects causing cessation of β -blockers occurred in 31 of the 257 persons (12%). At 32-month follow-up, use of β -blockers caused a 53% significant independent reduction in the incidence of new coronary events in elderly persons with PAD and prior myocardial infarction [129]. In a vascular surgery clinic, 301 of 364 persons (83%) with PAD and CAD were treated with β -blockers [124]. β -Blockers should be used to treat CAD in patients with PAD in the absence of contraindications to these drugs (Table III).

Statins

On the basis of data from the Heart Protection Study, persons with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels [98] (Table III). Three double-blind, randomized, placebo-controlled studies have also demonstrated that statins improve walking performance in persons with PAD [105-107].

In a study of 69 persons, mean age 75 years, with intermittent claudication, a mean ABI of 0.63, and a serum LDL cholesterol of 125 mg/dl or higher, 3 of 34 persons (9%) treated with simvastatin and 6 of 35 persons (17%) treated with placebo died before the 1-year study was completed [105]. Compared with placebo, simvastatin significantly increased treadmill exercise time until the onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after therapy [105].

In a study of 354 persons, mean age 68 years, with intermittent claudication and hypercholesterolemia, at 1-year follow-up, compared with placebo, atorvastatin 80 mg daily significantly improved pain-free treadmill walking distance by 40% and significantly improved community-based physical activity [106]. In a study of 86 persons, mean age 67 years, with intermittent claudication and hypercholesterolemia, at 6-month follow-up, compared with placebo, simvastatin 40 mg daily significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ABI at rest and after exercise, and significantly improved symptoms of claudication [107].

Statin use is also associated with superior leg functioning independent of cholesterol levels and other potential confounders [130]. The data suggest that non-cholesterol-lowering properties of statins may favorably influence functioning in persons with and without PAD [130].

Drugs to increase walking distance

Chelation therapy has been documented to be ineffective in the therapy of PAD [131]. Numerous drugs have been demonstrated to be ineffective in improving walking distance in persons with intermittent claudication [132, 133]. Beraprost sodium, an orally active prostaglandin I₂ analogue, was demonstrated to be no more effective than placebo in persons with intermittent claudication [134]. Naftidrofuryl [135] and propionyl levocarnitine [136] have been reported to improve exercise walking distance in persons with intermittent claudication but have not been approved for use in the United States [132].

Two drugs, pentoxifylline and cilostazol, have been approved by the United States Food and Drug Administration for symptomatic treatment of intermittent claudication. However, many studies have found no consistent improvement with pentoxifylline in patients with intermittent claudication in comparison with placebo [137-139]. In a vascular surgery clinic, 301 of 301 persons (100%) with intermittent claudication were treated with cilostazol or pentoxifylline [124].

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been documented in numerous trials to improve exercise capacity in patients with intermittent claudication [133, 140-143], and in a dose of 100 mg twice daily, was shown to be superior to both placebo and pentoxifylline [142].

Cilostazol should be given to patients with PAD to increase walking distance (Table III) but should not be given to persons with PAD who also have heart failure. Other contraindications to the use of cilostazol include a creatinine clearance < 25 ml/min, a known predisposition for bleeding, or coadministration of CYP3A4 or CYP2C19 inhibitors such as cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole, and HIV-1 protease inhibitors.

Exercise rehabilitation programs

Exercise rehabilitation programs have been shown to increase walking distance in persons with intermittent claudication through improvements in peripheral circulation, walking economy, and car-

diopulmonary function [144, 145]. The optimal exercise program for improving claudication pain distance in persons with PAD uses intermittent walking to near-maximal pain during a program of at least 6 months [146]. Strength training is less effective than treadmill walking [147]. The ACC/AHA guidelines recommend a supervised exercise program for patients with intermittent claudication [7] (Table III).

Supervised exercise training is recommended for a minimum of 30-45 min in sessions performed at least 3 times per week for a minimum of 12 weeks [7] and preferably for 6 months or longer [146]. Among persons with PAD, self-directed walking exercise performed at least 3 times weekly is associated with significantly less functional decline during the subsequent year [148].

Foot care

Persons with PVD must have proper foot care [7, 149] (Table III). They must wear properly fitted shoes. Careless nail clipping or injury from walking barefoot must be avoided. Feet should be washed daily and the skin kept moist with topical emollients to prevent cracks and fissures, which may have portals for bacterial infection. Fungal infection of the feet must be treated. Socks should be wool or other thick fabrics, and padding or shoe inserts may be used to prevent pressure sores. When a wound of the foot develops, specialized foot gear, including casts, boots, and ankle foot orthoses may be helpful in unweighting the affected area [149].

Lower extremity angioplasty and bypass surgery

Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are: 1) incapacitating claudication in persons interfering with work or lifestyle; 2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence [150]. Percutaneous transluminal angioplasty can be performed if there is a skilled vascular interventionalist and the arterial disease is localized to a vessel segment less than 10 cm in length [141]. Compared to percutaneous transluminal angioplasty alone, stenting improves 3-year patency by 26% [151]. Patients treated with drug-eluting stents should be treated with aspirin plus clopidogrel for at least 1 year. After infrainguinal bypass surgery, oral anti-coagulant therapy is preferable in persons with venous grafts, whereas aspirin is preferable in persons with nonvenous grafts [152].

Percutaneous balloon angioplasty and/or stenting is indicated for short-segment stenoses, whereas multisegment disease and occlusions are most effectively treated with surgical revascularization

[153]. Revascularization of PAD is discussed extensively elsewhere [7, 149]. In patients presenting with severe limb ischemia caused by infra-inguinal disease and who are suitable for either surgery or angioplasty, by-pass surgery and balloon-angioplasty are associated with similar outcomes in terms of amputation-free survival [154]. Patients with intermittent claudication should be considered for revascularization to improve symptoms only in the absence of other disease that would limit exercise improvement such as angina pectoris, heart failure, chronic pulmonary disease, or orthopedic limitations [7].

Amputation

Nonrandomized studies have shown that both immediate and long-term survival are higher in patients having revascularization rather than amputation for limb-threatening ischemia [155, 156]. However, amputation of lower extremities should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage [149].

The European Society of Cardiology guidelines on the diagnosis and treatment of PAD were recently published online in the August 26, 2011 issue of the *European Heart Journal* [157]. I concur with these excellent guidelines and recommend that all physicians should read them.

Future research needs to be performed investigating the role of inflammation in the pathogenesis of PAD. Additional therapies are needed to improve the quality of life and outcomes in patients with PAD. Further research is needed in angiogenesis gene therapy and stem cell or progenitor cell therapy in patients with critical limb ischemia.

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